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Amyotrophic Lateral Sclerosis Mortality in 1.9 Million US Cancer Survivors

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Key Words

Amyotrophic lateral sclerosis · Parkinson's disease · Cancer · Melanoma · Lymphoproliferative · Registry · Smoking · Tobacco

Abstract

Background: Large cancer registries offer the opportunity to explore and generate hypotheses about the pathogenesis of cancer and other diseases, including neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). ***Methods:*** Using data from nine population-based cancer registries of the Surveillance, Epidemiology, and End Results (SEER) Program of the US National Cancer Institute (NCI) and death certificates, we followed 1.9 million cancer survivors who were diagnosed between 1973 and 2000 and who survived at least 1 year, through the year 2000. The outcome of interest was the standardized mortality ratio (SMR) of observed to expected ALS deaths among cancer survivors. To assess the validity of the study design, we also examined associations with Parkinson's disease mortality, which we expected to be inversely associated with smoking-related cancers. ***Results:*** There was no significantly increased risk or deficit of ALS mortality for all cancer sites combined (SMR = 1.0). Parkinson's disease mortality was, as expected, significantly and inversely associated with smoking-related cancers. Both ALS and Parkinson's disease mortality were significantly elevated following melanoma (SMR = 1.6; 95% CI = 1.1–2.2; SMR = 1.5; 1.2–1.8, respectively). Contrary to previous hypotheses, ALS was unrelated to lymphomas or lymphoproliferative malignancies and was not associated with smoking-related cancers. ***Conclusions:*** In this exploratory study, we observed a modest, significant association between melanoma and both ALS and Parkinson's disease mortality. It would be useful to explore these findings in other large national databases that are able to link cancer and ALS and Parkinson's disease.

Amyotrophic lateral sclerosis (ALS), a disease involving progressive degeneration of motor neurons, is of largely unknown etiology [1]. This study was designed to generate new hypotheses about the pathogenesis of ALS as well as to explore existing findings related to ALS and cancer in a large population-based setting. For example, our analysis was intended to examine associations with lymphoproliferative cancers, which case reports suggest may be related to ALS [1], and evaluate linkage to smoking-related cancers because a few case-control studies and one cohort study have found positive associations between ALS and smoking [2–4]. Although epidemiologic studies that have examined the relationship between ALS and cancer have found no association, most include

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either small numbers of persons with ALS or with cancer [5–9].

We evaluate the risk of death due to ALS (n = 560) among 1.9 million cancer patients reported to population-based cancer registries that participate in the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) Program. Our findings are contrasted in the same database to reported mortality due to Parkinson's disease (n = 1,985). Parkinson's disease is included in the analysis to help assess study design. Because prior cohort studies of cancer in patients with this disorder have shown an inverse association with tobacco-related cancers [10–13], similar relationships in this analysis would support the validity of the study design.

Methods

The SEER Program has compiled incidence data on invasive cancer since 1973 in nine population-based registries, including five states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and four metropolitan areas (Atlanta, Detroit, San Francisco, and Seattle) [14]. Data collected include primary tumor site, morphology, and stage at diagnosis; and patients are followed annually for survival status. The population covered by the nine SEER registries (about 10% of the population) [15] is considered comparable to the general population with regard to education and poverty level [14]. Quality assurance is maintained through on-site monitoring, data editing, case-finding audits, reabstracting of cases and various educational programs [16]. Standards have established a case ascertainment rate of 98%, a follow-up rate of 95% [16], and an overall microscopic diagnostic confirmation rate of more than 98%.

In this study all patients who survived at least one year were followed through December 31, 2000. The study was limited to whites because of the small numbers of ALS deaths among other ethnic groups. Person-years at risk were accumulated for each subject beginning 1 year after cancer diagnosis to exclude the initial postdiagnosis period when the likelihood of reporting a noncancer cause of death might be artificially reduced. Person-years were counted until the date of death, date last known alive, date lost to follow-up or December 31, 2000, whichever occurred first. Cause of death in SEER was provided by each state's vital records department. We validated the death certificates for ALS deaths following acute leukemia in Connecticut because of a high number of ALS deaths following a diagnosis of acute myelogenous leukemia (AML). We excluded the one AML and one acute lymphocytic leukemia (ALL) case in which the death certificates were erroneously coded as ALS (rather than as AML and ALL) and that met the one-year postdiagnosis study inclusion requirement. There were no other ALS deaths more than one year following a diagnosis of AML or ALL in the study from any other registry.

We characterized observed deaths due to ALS (as an underlying cause of death) among subjects in the SEER database based on the classifications ICD-8:348.0, ICD-9:335.2, and ICD-10:G12.2, although the latter two categories correspond to motor neuron disease (MND). ALS is, however, the predominant subtype, which represents about 90% of MND deaths [6]. Deaths due to Parkinson's disease were based on classifications ICD-8:342.9, ICD-9:332.0, and ICD-10:G20. The expected number of deaths from ALS and Parkinson's disease was calculated by applying the 5-year age, 5-year calendar period, and sex-specific mortality rate for ALS and for Parkinson's disease in the nine SEER registry regions to the person-years at risk for each type of cancer diagnosis in the SEER database. We then calculated the standardized mortality ratio (SMR) for each cancer site as the ratio of the observed number of deaths of ALS and of Parkinson's disease to the expected number of deaths and calculated 95% confidence intervals (CI), assuming a Poisson distribution of the observed deaths. We reported mortality risks for all cancer sites for which there were two or more deaths from ALS. We also reported mortality risks for hematopoietic and lymphoproliferative cancers combined (leukemia, Hodgkin's disease, Non-Hodgkin's lymphoma and multiple melanoma) and tobacco-related cancers (buccal and pharyngeal, pancreatic, laryngeal, lung, cervix, kidney parenchyma, and bladder cancers). The latter were also calculated by gender because a recent cohort study observed an elevated risk of ALS mortality associated with smoking in women, although not in men [4].

For all cancer sites combined (excluding nonmelanoma skin cancer, which is not ascertained in SEER), the average duration of follow-up after cancer was 7.1 years in the ALS study, and 8.5 years for Parkinson's disease, with a total of 8.3 million person-years of follow-up for each outcome.

Results

The overall risk of death due to ALS (SMR = 1.0; 95% CI = 0.9–1.1) was not increased among the one-year survivors of all cancers combined (table 1). Mortality risk was not significantly elevated in either specific hematopoietic or lymphoproliferative cancers or the combined group of these malignancies (SMR = 1.2). There was also no elevated risk in the combined group of tobacco-related cancers for both sexes combined (SMR = 1.0), or for men (SMR = 0.9; 95% CI = 0.7–1.2) and women (SMR = 1.1; 95% CI = 0.8–1.6). The mortality risk of ALS was, however, significantly increased after cancer of the tongue (SMR = 2.7) and melanoma (SMR = 1.6), the latter representing 32 cases.

Although there was a significant deficit in risk of mortality due to Parkinson's disease after cancer (SMR = 0.9; 95% CI = 0.9–1.0), the deficit was accounted for by the reduced risk of Parkinson's disease mortality after tobacco-related cancers. Tobacco-related cancers as a group were associated with a significant 20% reduced risk of Parkinson's disease mortality, and Parkinson's disease mortality after lung cancer occurred at rates that were 40% below expected. Only melanoma was related to a significantly increased risk of Parkinson's disease mortality (SMR = 1.5).

Table 1. SMR for ALS and Parkinson's disease mortality among cancer survivors in the SEER Program

Cancer site	ALS			Parkinson's disease		
	obs.	exp.	SMR (95% CI)	obs.	exp.	SMR (95% CI)
All cancers (excluding nonmelanoma skin)	560	553.3	1.0 (0.9–1.1)	1,985	2,103.5	0.9 (0.9–1.0)*
All buccal and pharynx	21	16.4	1.3 (0.8–2.0)	56	54.8	1.0 (0.8–1.3)
Lip	9	5.3	1.7 (0.8–3.3)	23	22.9	1.0 (0.6–1.5)
Tongue	7	2.6	2.7 (1.1–5.7)*	4	7.4	0.5 (0.2–1.4)
Salivary gland	2	1.6	1.3 (0.1–4.5)	4	5.4	0.7 (0.2–1.9)
Floor of mouth	2	1.8	1.1 (0.1–4.1)	6	4.3	1.4 (0.5–3.0)
Colon	58	59.4	1.0 (0.7–1.3)	228	227.7	0.8 (0.7–0.9)*
Rectum	15	16.4	0.9 (0.5–1.5)	50	65.4	0.8 (0.6–1.0)
Rectosigmoid junction	10	9.0	1.1 (0.5–2.0)	30	37.0	0.8 (0.6–1.2)
Stomach	4	4.0	1.0 (0.3–2.6)	10	17.3	0.6 (0.3–1.1)
Larynx	12	9.5	1.3 (0.7–2.2)	20	30.5	0.7 (0.4–1.0)
Bronchus and lung	21	22.4	0.9 (0.6–1.4)	41	64.9	0.6 (0.5–0.9)*
Female breast	107	104.3	1.0 (0.8–1.2)	270	272.0	1.0 (0.9–1.1)
Uterine	46	39.47	1.2 (0.9–1.6)	87	95.0	0.9 (0.7–1.1)
Ovary	3	6.9	0.4 (0.1–1.3)	16	13.7	1.2 (0.7–1.9)
Cervix	4	5.5	0.7 (0.2–1.9)	7	9.6	0.7 (0.3–1.5)
Vulva, clitoris	2	1.7	1.2 (0.1–4.4)	4	5.9	0.7 (0.2–1.7)
Prostate	112	124.3	0.9 (0.7–1.1)	726	686.6	1.1 (1.0–1.1)
Testis	3	1.8	1.7 (0.3–5.0)	3	2.0	1.5 (0.3–4.5)
Urinary bladder	41	43.3	1.0 (0.7–1.3)	161	192.5	0.8 (0.7–1.0)*
Kidney parenchyma/renal pelvis	10	11.4	0.9 (0.4–1.6)	42	38.9	1.1 (0.8–1.5)
Melanoma of the skin	32	20.2	1.6 (1.1–2.2)*	87	58.8	1.5 (1.2–1.8)*
Other nonepithelial skin	3	1.6	1.9 (0.4–5.6)	10	6.4	1.6 (0.8–2.9)
Brain	2	0.8	2.6 (0.3–9.3)	3	0.9	3.2 (0.6–9.4)
Connective tissue cancer	4	2.5	1.6 (0.4–4.1)	8	8.4	1.0 (0.4–1.9)
Thyroid	7	6.1	1.1 (0.5–2.4)	6	11.5	0.5 (0.2–1.1)
All leukemia	14	9.8	1.4 (0.8–2.4)	34	36.0	0.9 (0.7–1.3)
Chronic lymphocytic leukemia	11	7.5	1.5 (0.7–2.6)	29	29.2	1.0 (0.7–1.4)
Non-Hodgkin's lymphoma	18	16.0	1.1 (0.7–1.8)	37	50.7	0.7 (0.5–1.0)
Hodgkin's disease	0	1.8	–	4	3.2	1.3 (0.3–3.2)
Multiple myeloma	4	3.1	1.3 (0.4–3.3)	10	10.1	1.0 (0.5–1.8)
Hematopoietic and lymphoproliferative cancers[1]	36	30.7	1.2 (0.8–1.6)	85	100.0	0.9 (0.7–1.1)
Tobacco-related cancers[2]	109	109.4	1.0 (0.8–1.2)	330	394.2	0.8 (0.8–0.9)*
Cancers other than tobacco-related cancers	451	443.9	1.0 (0.9–1.1)	1,655	1,709.3	1.0 (0.9–1.0)

ALS = Amyotrophic lateral sclerosis; obs.= observed; exp.= expected.

* $p < 0.05$.

[1] Includes leukemia, Hodgkin's disease, Non-Hodgkin's lymphoma and multiple myeloma.

[2] Includes all buccal and pharynx, pancreas, larynx, bronchus and lung, cervix, kidney parenchyma and bladder cancer.

Discussion

This study was designed to evaluate the associations between cancer at specific sites and ALS mortality. Our major results on the relationship between Parkinson's disease and cancer are generally consistent with previous epidemiologic studies and support the validity of the study design. Several studies that assessed the cancer risk among parkinsonian patients also reported a lower risk of cancer than in the general or control population [10–13]. These studies also found a risk for tobacco-related cancers that was lower than expected. Finally, two studies that assessed risk for individual cancer sites also found a significantly increased risk for melanoma [11, 13], although one did not [10]. Levodopa treatment for Parkinson's disease has been hypothesized to increase the risk of melanoma [11], but the relationship is controversial [17]. If levodopa contributed to the increase in Parkin-

son's disease mortality risk following melanoma in this series, it would mean that treatment for Parkinson's disease often preceded the melanoma diagnosis. We have no basis, however, for determining whether or when such treatment occurred.

We found no association between overall cancer incidence and ALS mortality. There was also no relationship with hematopoietic and lymphoproliferative cancers, contrary to prior series from tertiary care centers [1]. Although the low incidence of ALS limits the power to find such an association, the study suggests that the magnitude of any association in these registries is unlikely to be large, given the 1.6 upper limit to the confidence interval. We also detected no relationship between ALS and smoking-related cancers, neither in men nor women. While only indirect evidence, the results are inconsistent with the positive smoking findings of other ALS observational studies [2–4]. The association between tongue cancer and ALS is based on only 7 cases, with 5 occurring within 5 years of the cancer diagnosis. The short time from tongue cancer to ALS death suggests early detection of the tongue cancers in the course of ALS care.

We considered whether the apparent modest excess risk of ALS after melanoma may reflect chance (due, for example, to multiple comparisons) or possibly ascertainment bias. The fact that the risk of ALS mortality continued to be increased 5 (SMR = 1.7, n = 10) and 10 years (SMR = 1.4, n = 10) after melanoma, however, argues against bias due to early medical screening after the ALS diagnosis. On the other hand, in those diagnosed with melanoma and ALS, the high male to female sex ratio, 1.7, and the high median age at the time of melanoma diagnosis, 63.4, is more reflective of ALS [18] than melanoma, and therefore does not support a risk factor hastening the incidence of both diseases. If, however, the association reflects common causal factors, it may relate to the shared embryonic lineage of neurons and melanocytes in neural crest cells [19]. A more specific possibility is that the two diseases may involve the role of metabotropic glutamate receptors in both motor neurons and melanocytes. Metabotropic glutamate receptors (mGluRs), specifically group 1 mGluRs, have been implicated in the selective vulnerability of human motor neurons in the spinal cord [20], and recent studies indicate that group 1 mGluRs may contribute to the control of human melanocyte proliferation [21], and melanocytic neoplasia in mice [22].

This study of cancer and ALS is exploratory. Its most notable limitation is its reliance on death certificates for the cause of death in a context where the earlier cancer is a potentially competing cause of death. Although death certificates are less reliable than other medical records and may vary by geographic area [23], several studies, although not all [24], have determined that death certificates are reasonably accurate at identifying MND or ALS in a number of industrialized countries [25, 26]. In any case, comparison rates are derived from death certificates as well. Because the original cancer diagnosis might lead to an underreporting of ALS as the cause of death, the resulting misclassification would tend to diminish, rather than heighten, associations with cancer sites. Thus, the underreporting of ALS makes less likely the finding of false positive results, but undermines the detecting of true positive associations, as well. A further drawback is the limited ability to detect associations with cancers that have high fatality or low incidence rates resulting in low numbers of person-years at risk.

Although based on morbidity/mortality data with limited covariate information, this study provides no evidence of a relationship between ALS mortality and all cancer sites combined. Nor does it corroborate that cigarette smoking is a risk factor for ALS or the relationship to lymphoproliferative cancers. The modest relationship between melanoma and ALS and of Parkinson's disease mortality is intriguing. It would be useful to explore these findings in other large national databases that are able to link cancer and ALS and Parkinson's disease. The power of this and future epidemiologic studies is to generate new hypotheses about the pathogenesis of ALS.

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